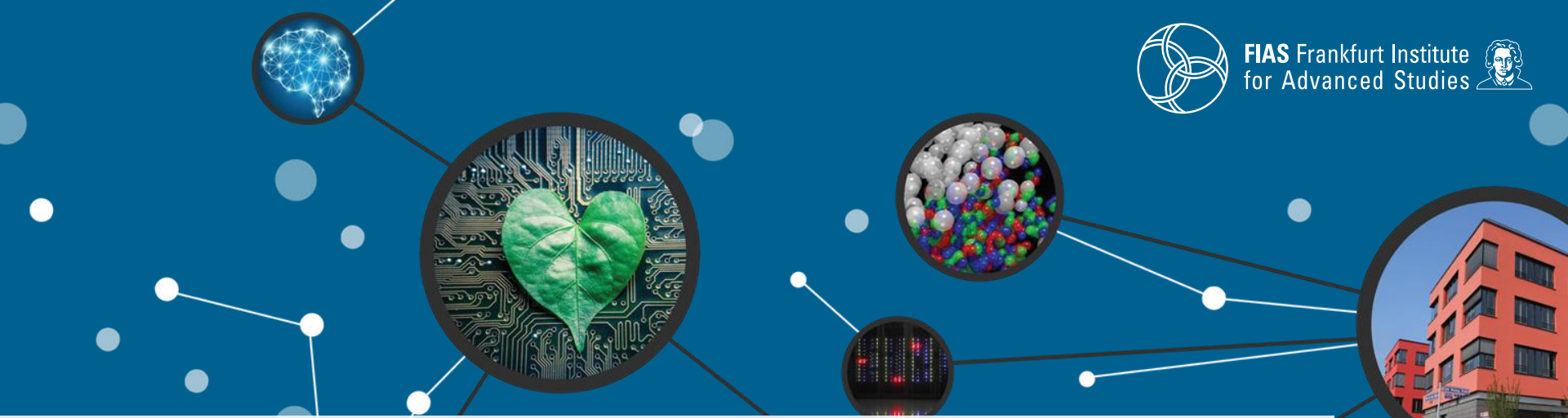


FIAS Frankfurt Institute for Advanced Studies

Coarse-Grained Modeling of Salbutamol and Salmeterol Binding to β2-Adrenergic Receptor

Cristina Gil Herrero, Sebastian Thallmair
PhD student
gil@fias.uni-frankfurt.de

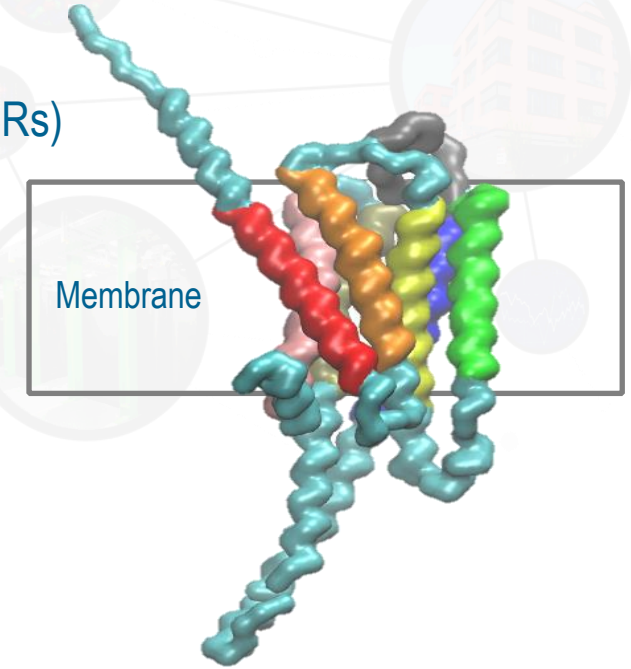
Outline

1. Introduction
2. Ligand Parametrization
3. Ligand Behaviour in the Membrane
4. Protein Parametrization
5. Ligand and Protein the Membrane
6. Binding Pocket Placement
7. Binding Events
8. Conclusions and Future Perspectives

1. Introduction

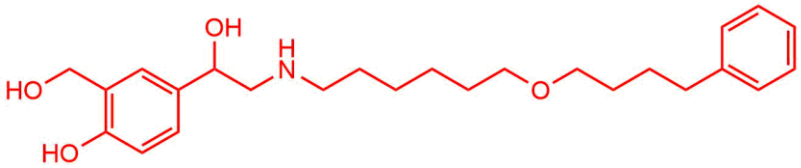
GPCRs: β2-adrenergic receptor (**B2AR**)

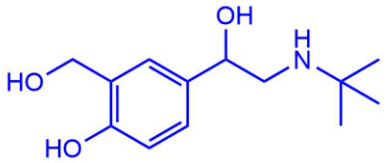
- Belongs to the family **G protein-coupled receptors** (GPCRs)
- GPCRs are integral **membrane proteins**
- 7 transmembrane domains
- Mainly located in **airway smooth muscles**



β2-adrenergic receptor agonists: salmeterol (**SALMT**) and salbutamol (**SALBT**)

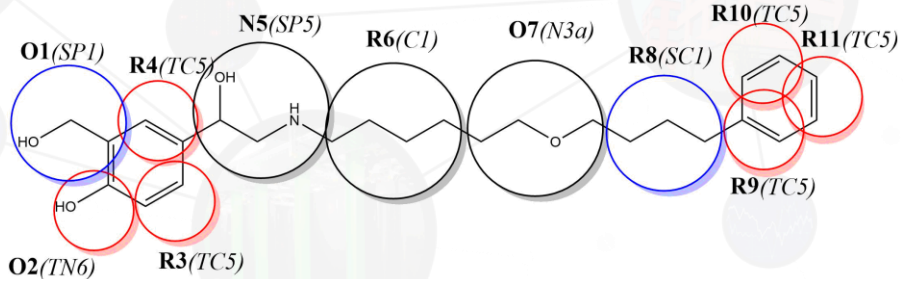
- **Drugs** employed in the treatment of respiratory diseases
- High **affinity** to B2AR
- **Binding** pathways have **not** yet been fully **characterized**

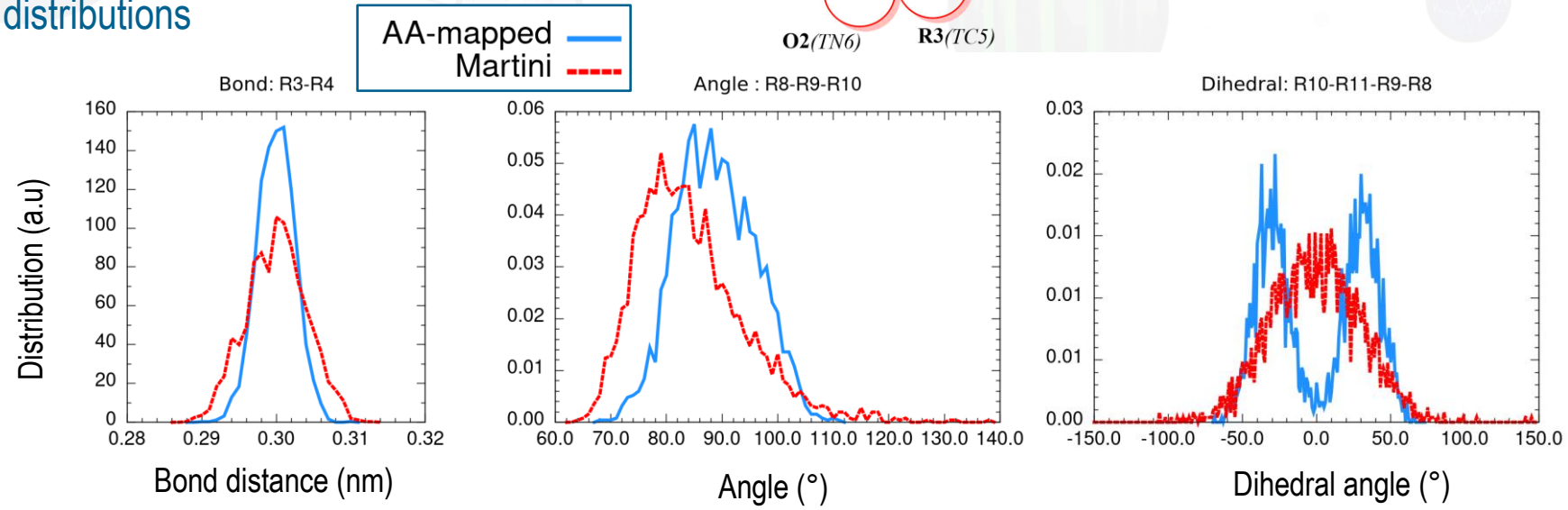




2. Ligand Parametrization

- **All-atom** (AA) simulation as reference
- Define **type** and **amount** of CG beads
- Reproduce **bond**, **angle** and **dihedral** distributions





2. Ligand Parametrization

- Account for **symmetry** and **volume**
- Check the performance in an organic solvent
- Comparison with **experimental** partition coefficient

SASA values

AA

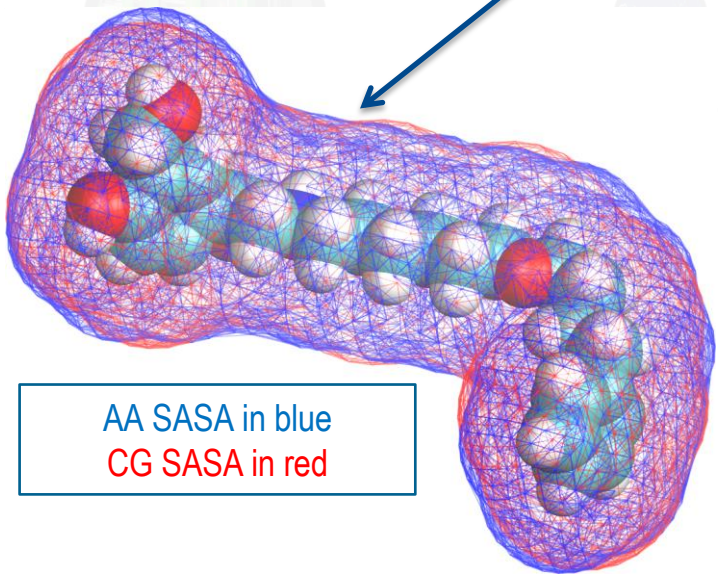
Avg: 9.27 ± 0.60 nm^2

CG

Avg: 9.19 ± 0.38 nm^2

Good agreement of the

Solvent Accesible Surface Area (SASA)



AA SASA in blue

CG SASA in red

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CG

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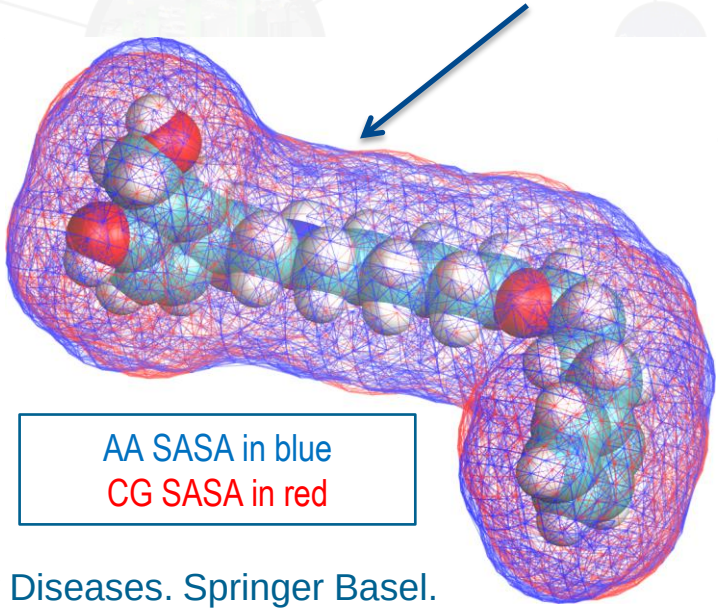
Hydrated octanol/water free energy of transfer:

Experimental(1)	24.12 kJ/mol
Obtained value	24.40 kJ/mol

Good agreement of the Solvent Accesible Surface Area (SASA)



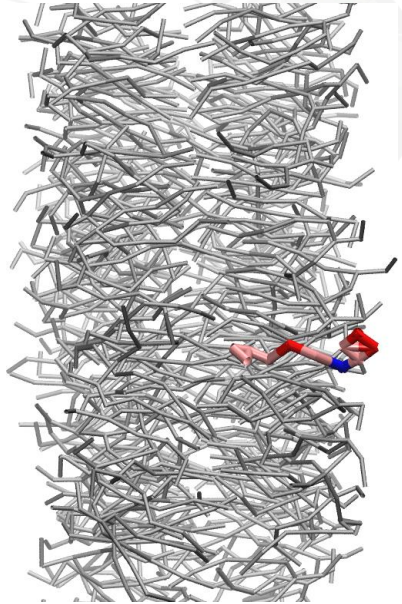
AA SASA in blue
CG SASA in red

(1)Parnham, Michael, ed. (2015) Encyclopedia of Inflammatory Diseases. Springer Basel. doi: 10.1007/978-3-0348-0620-6

3. Ligand Behaviour in the Membrane

Salmeterol

- The 10 SALMT ligands **remain in the leaflet** they first entered
- **Do not diffuse** into water
- Do not change leaflet



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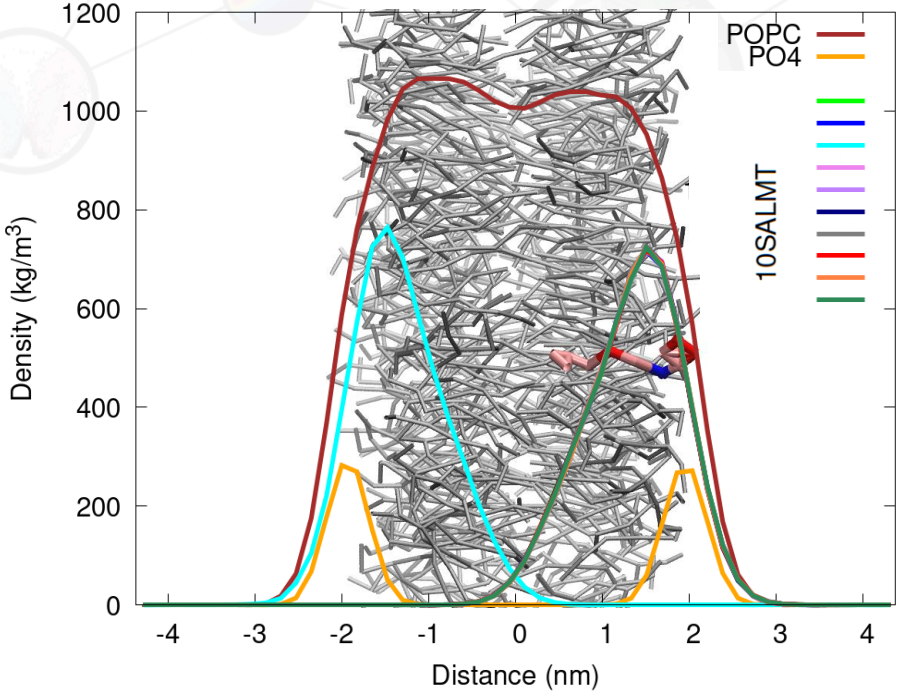
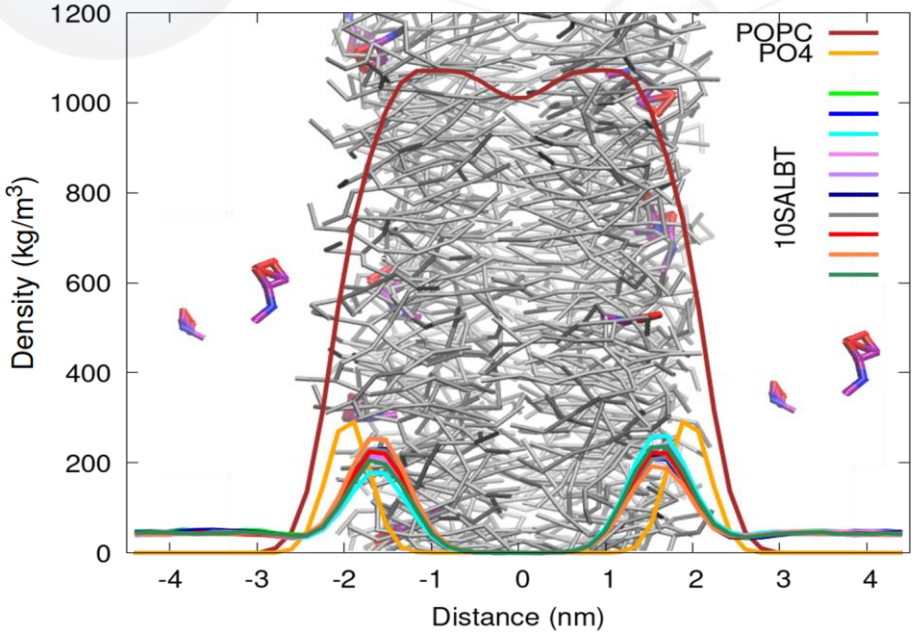


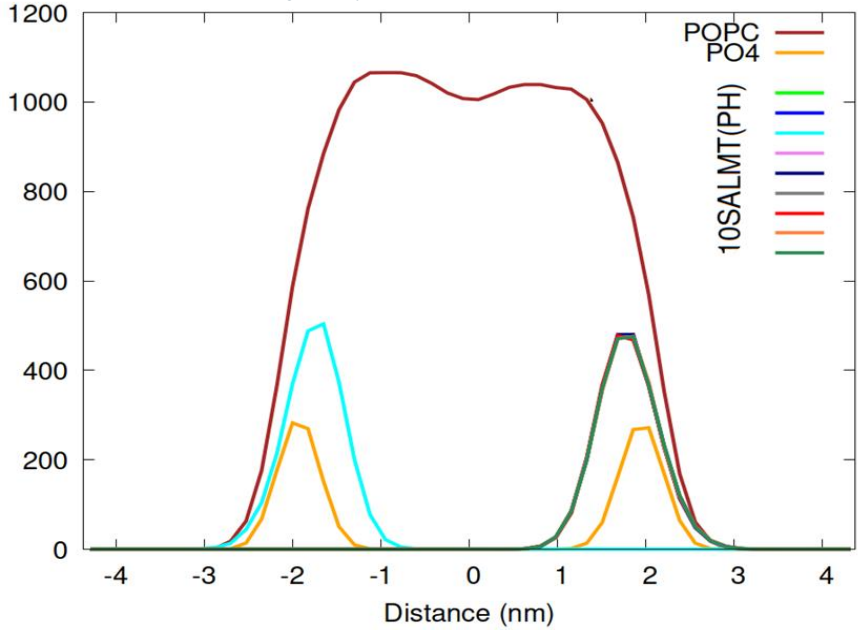
3. Ligand Behaviour in the Membrane

Salbutamol

- SALBT molecules **diffuse** along the membrane and the solvent
- Polar head group resides at **similar membrane depth** for both molecules



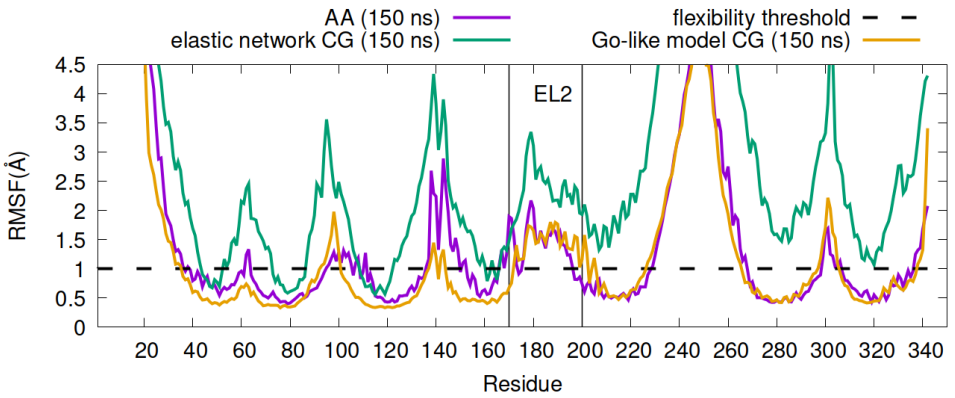
*Considering only polar head of SALMT molecules



4. Protein Parametrization

- Structure obtained from **Alpha Fold**
- Two possibilities for reproducing the secondary structure:
  Elastic network vs **Gō-like model**

Flexibility comparison with AA



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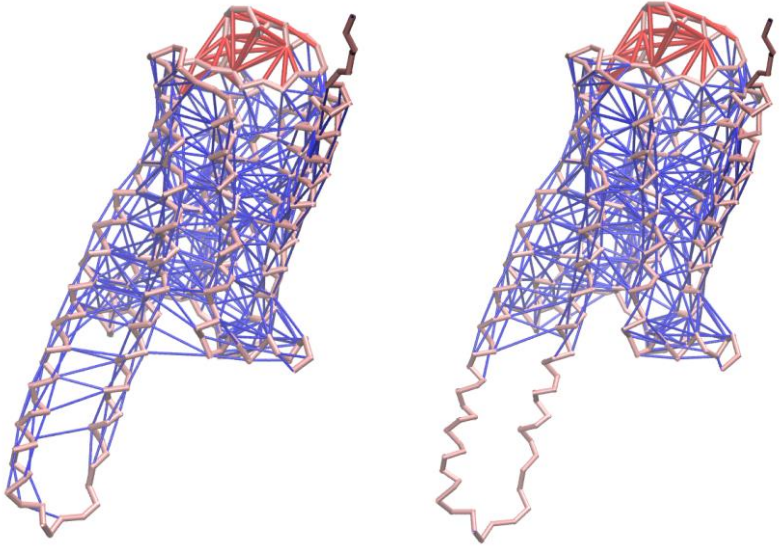

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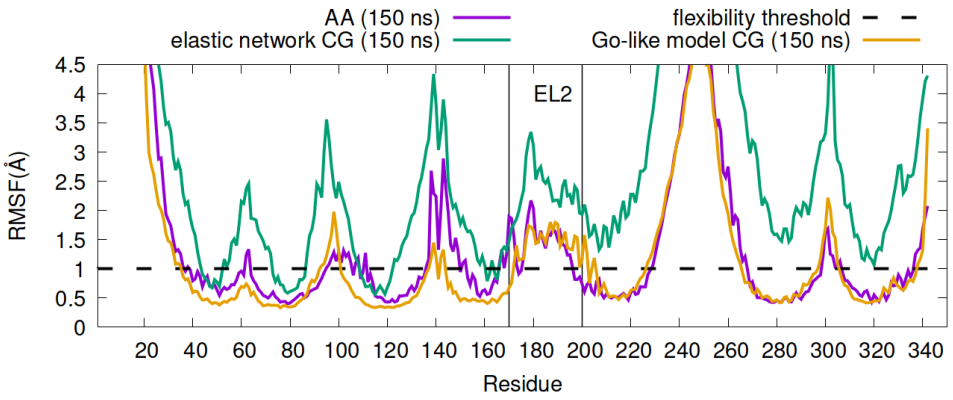


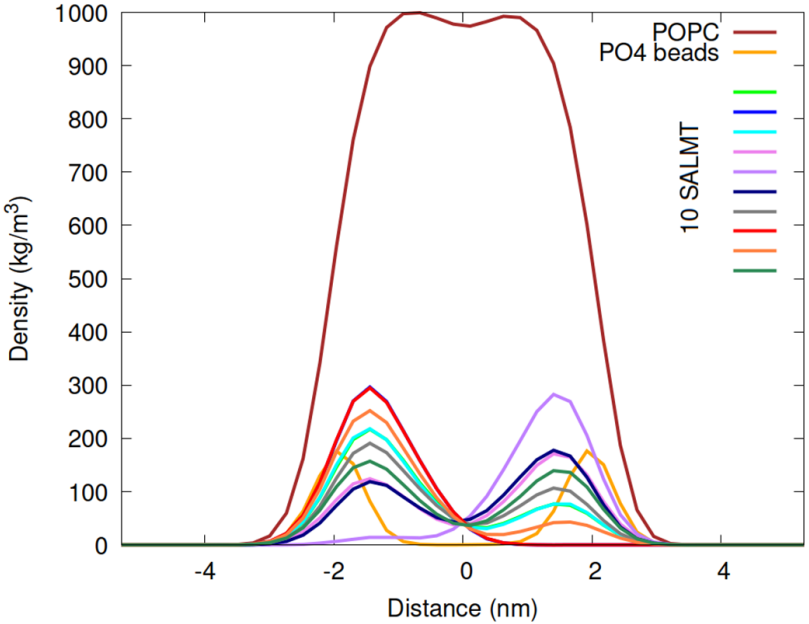
Gō-like model interactions with different **contact maps** (experimental PDB vs AF structures)

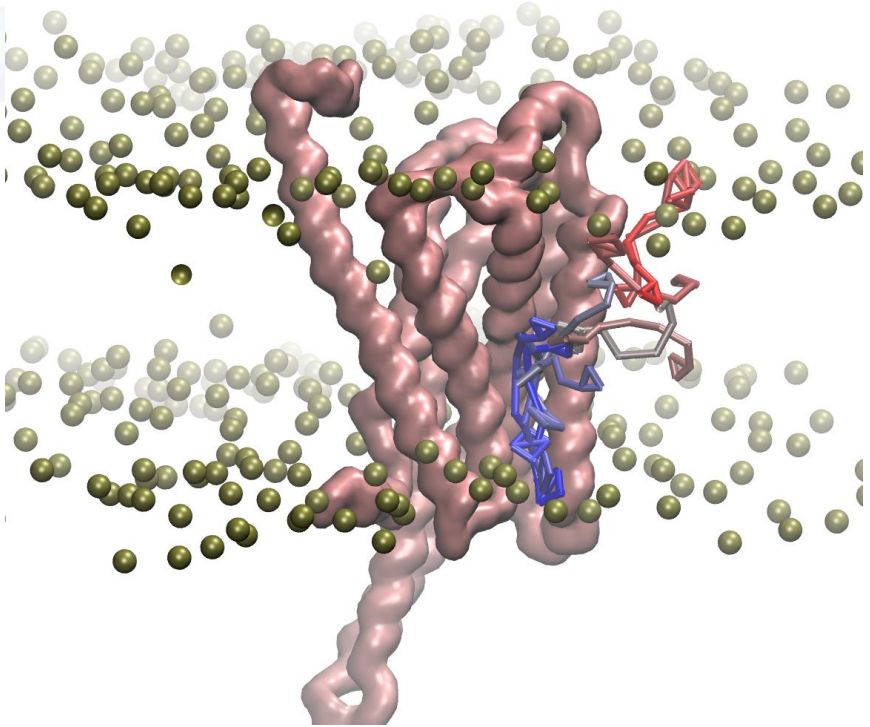
- **ε** values were tested (8.0,10.0,12.0, 14.0 kJ/mol) **12.0 kJ/mol** represented best the AA flexibility

5. Ligand and Protein in the Membrane

Salmeterol, B2AR and POPC membrane

- The protein enables **“flip-flops”** in the bilayer



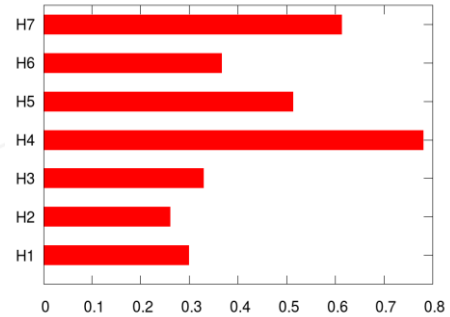


5. Ligand and Protein in the Membrane

Salmeterol, B2AR and POPC membrane

- Analysis of the **contacts** between B2AR and SALMT
- Similar trends are found in several transmembrane domains: H4, H5, H7

Average domain contacts:



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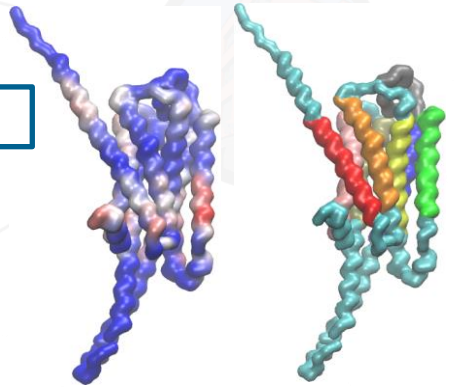

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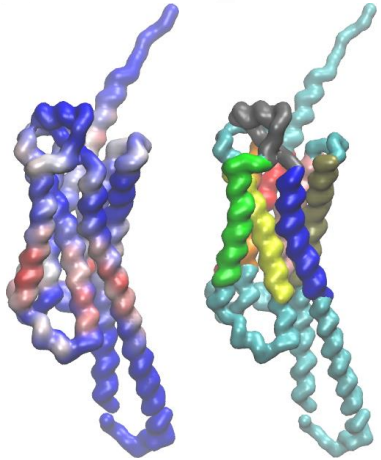
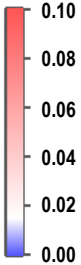
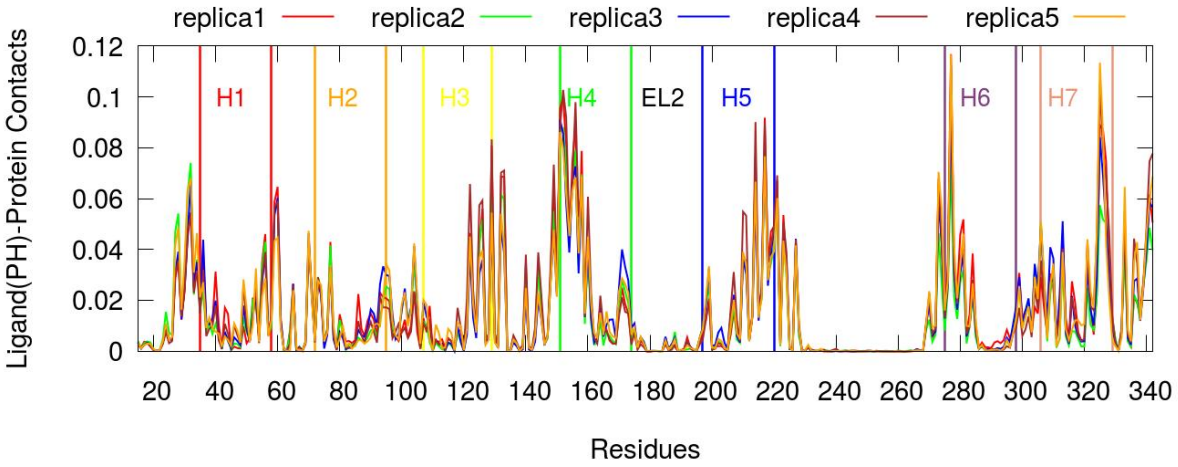


Color Scale:

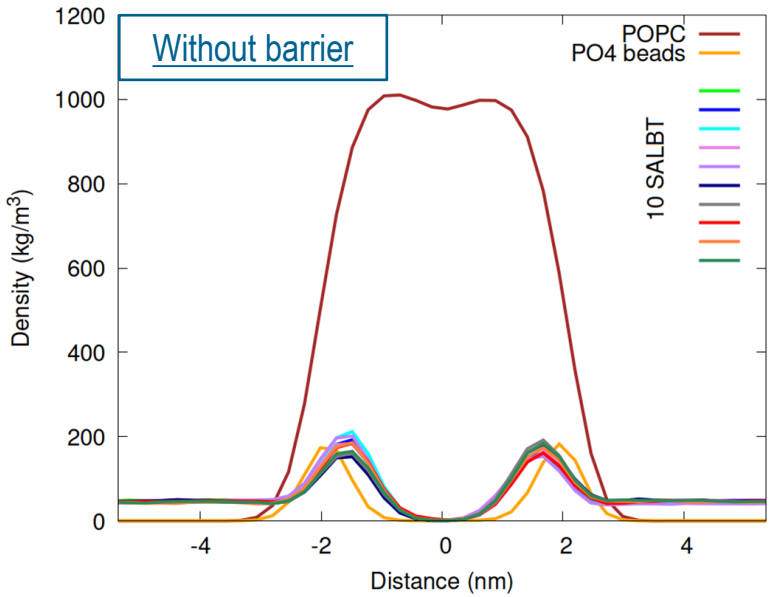


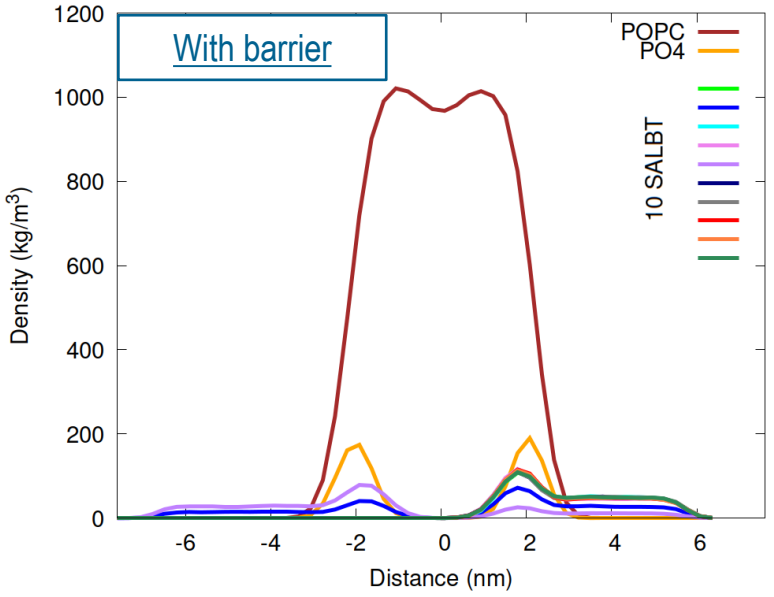


5. Ligand and Protein in the Membrane

Salbutamol, B2AR and POPC membrane

- **"Flip-flops"** are not occuring that often as for SALMT
- **Similar density** trend as without the protein

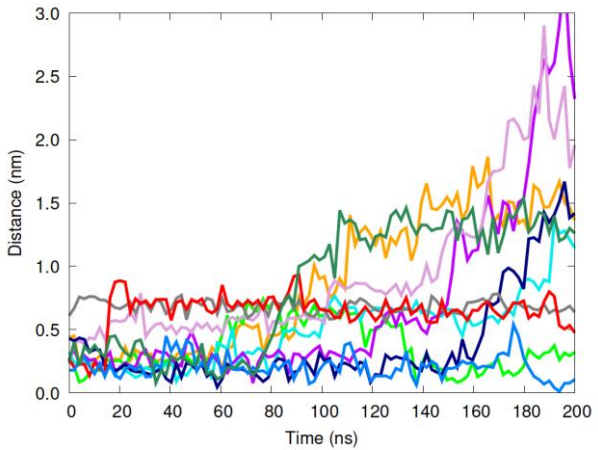




6. Binding Pocket Placement

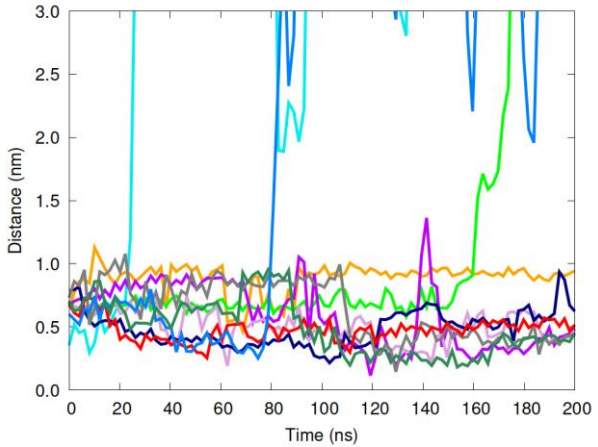
Salmeterol

- In most replicas, SALMT **remained in the BP** for the 200 ns of simulation
- Confirming the **high affinity** of the ligand for the BP



Salbutamol

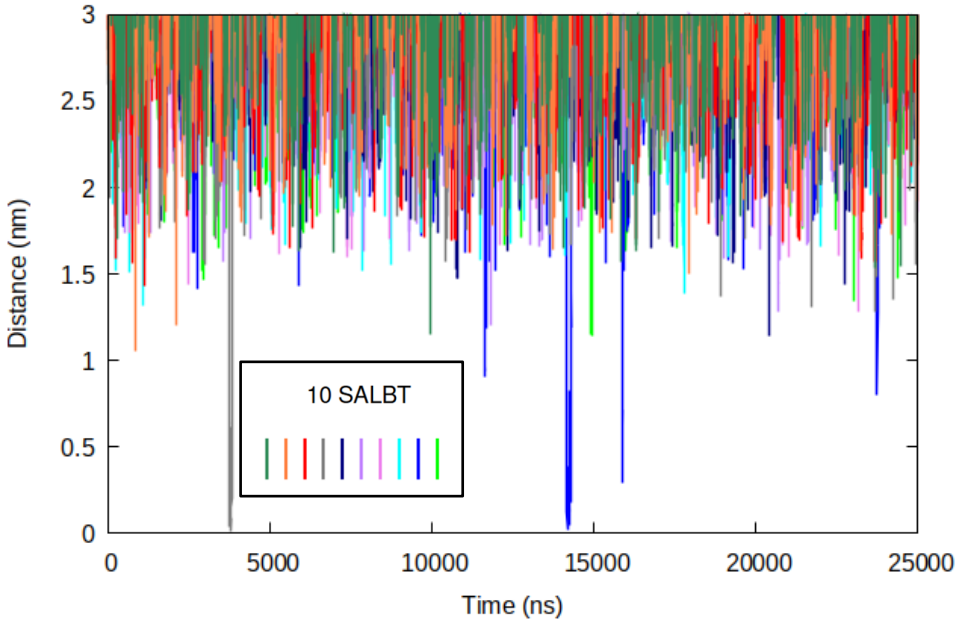
- A higher proportion of SALBT leaves the BP
- However, more than 50% remain
- Confirming also its **high affinity**

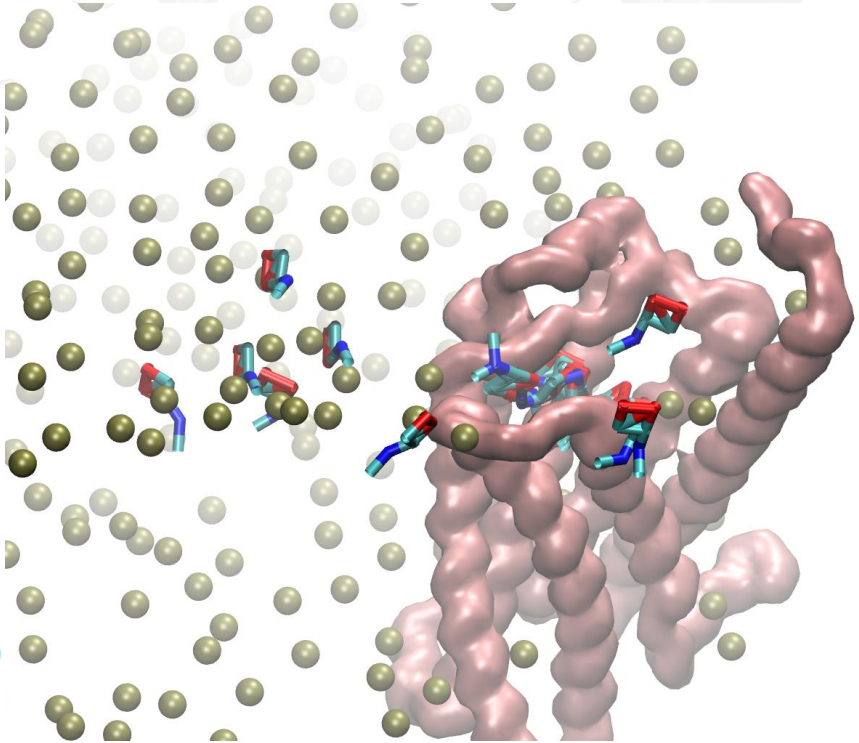


7. Binding Events

Salbutamol, B2AR and POPC membrane

- Binding events have already been observed for **SALBT**





8. Conclusions and Future Perspectives

- **SALMT stays** mainly in the membrane, **SALBT** also enters the **water phase**
- Protein **flexibility** is **well reproduced** by the Gō-like model and allows binding
- Including B2AR, **“flip-flops” of SALMT** ligand take place
- First **binding** events observed for **SALBT**

- What enables “flip-flops” in SALMT?
- Why occurs “flip-flop” rarely in the case of SALBT compared to SALMT?
- What are the main binding pathways for each of the ligands? Do they mainly enter from the water phase? Or via the membrane?

Acknowledgments

Thanks for your attention!

CMMS